PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
10589-008-228		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US02/11758	11 APRIL 2002	11 APRIL 2001

International Patent Classification (IPC) or national classification and IPC
IPC(7): C12M 1/38, 1/40; C12Q 1/68 and US Cl.: 435/6, 91.2, 172.3, 286.1, 286.5, 282.2

Applicant
PTC THERAPEUTICS, INC.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   I [X] Basis of the report

   II [ ] Priority

   III [X] Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV [ ] Lack of unity of invention

   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI [ ] Certain documents cited

   VII [ ] Certain defects in the international application

   VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 NOVEMBER 2002	29 APRIL 2003
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer BENNETT CELSA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/11758

I. Basis of the report

1. With regard to the **elements** of the international application:*

- [ ] the international application as originally filed
- [X] the description:
  - pages (See Attached), as originally filed
  - pages _____, filed with the demand
  - pages _____, filed with the letter of _____
- [X] the claims:
  - pages (See Attached), as originally filed
  - pages _____, as amended (together with any statement) under Article 19
  - pages _____, filed with the demand
  - pages _____, filed with the letter of _____
- [X] the drawings:
  - pages (See Attached), as originally filed
  - pages _____, filed with the demand
  - pages _____, filed with the letter of _____
- [X] the sequence listing part of the description:
  - pages (See Attached), as originally filed
  - pages _____, filed with the demand
  - pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- [ ] contained in the international application in printed form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

- [X] the description, pages NONE
- [X] the claims, Nos. NONE
- [X] the drawings, sheets/fig NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/11758

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 1 (as amended on 15 Nov. 2002) and 2-18

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _ are so unclear that no meaningful opinion could be formed *(specify)*.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. (See Attached) .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1	NO
Industrial Applicability (IA)	Claims	1	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claim 1 lacks an inventive step under PCT Article 33(3) as being obvious over Kamb et al. US Pat. No. 6,060,240 in view of Hancock et al. US Pat. No. 5,716,825. Kamb et al. teach a method of screening a "test compound" (e.g. a nucleic acid) that binds a target RNA molecule by contacting a labeled target nucleic acid a library of support-bound nucleic acids (e.g. see Hancock col. 6) to form a hybridized complex and separating the detectably labeled hybridized complex using flow cytometry (e.g. FACS analysis)(e.g. see Hancock at col. 10-11). Although teaching the use of PCR primer amplification for determining the nature of the captured oligonucleotide support-bound sequence (e.g. see Hancock at col. 26)the Hancock reference fails to explicitly teach the use of PCR/Mass spectrometry. However, the Hancock et al. reference teaches the preferential use of PCR/mass spectroscopy (e.g. MALDI-TOF MS) for analysis of DNA samples (e.g. in hybridization assays)(See Hancock Abstract; col. 7-8). Accordingly, employing in the Kamb detection method of sample hybridized nucleic acid sequence., mass spec/PCR to improve nucleic detection as taught by Hancock would have been obvious due to the miniaturized and sensitive detection of such sequences as taught by the Hancock reference detection method.

It is noted that the amendment dated 15 November 2002 containing replacement pages 85-87 was not considered by the Examiner because the amendment broadened the scope of original claim 1 and introduced additional claim limitations in newly added claims 2-18 which were not searched in Chapter I.

Claim 1 (as originally filed) meets the criteria set out under PCT Article 33(2) and 33(3).

---------- NEW CITATIONS ----------

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-84, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) 85, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
85-87, filed with the letter of 15 November 2002.

This report has been drawn on the basis of the drawings,
page(s) NONE, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

III. NON-ESTABLISHMENT OF REPORT:

No international search report has been established for claim numbers 1 (as amended), 2-18.

WHAT IS CLAIMED IS:

1. A method for identifying a test compound that binds to a target RNA molecule, comprising the steps of:

(a) contacting a detectably labeled target RNA molecule with a library of solid support-attached test compounds under conditions that permit direct binding of the labeled target RNA to a member of the library of solid support-attached test compounds so that a detectably labeled target RNA:support-attached test compound complex is formed;

(b) separating the detectably labeled target RNA:support-attached test compound complex formed in step (a) from uncomplexed target RNA molecules and test compounds; and

(c) determining a structure of the test compound of the RNA:support-attached test compound complex.

2. The method of claim 1 in which the target RNA molecule contains an HIV TAR element, internal ribosome entry site, "slippery site", instability element, or adenylate uridylate-rich element.

3. The method of claim 1 in which the RNA molecule is an element derived from the mRNA for tumor necrosis factor alpha ("TNF-α"), granulocyte-macrophage colony stimulating factor ("GM-CSF"), interleukin 2 ("IL-2"), interleukin 6 ("IL-6"), vascular endothelial growth factor ("VEGF"), human immunodeficiency virus I ("HIV-1"), hepatitis C virus ("HCV" - genotypes 1a & 1b), ribonuclease P RNA ("RNaseP"), X-linked inhibitor of apoptosis protein ("XIAP"), or survivin.

4. The method of claim 1 in which the detectably labeled RNA is labeled with a fluorescent dye, phosphorescent dye, ultraviolet dye, infrared dye, visible dye, radiolabel, enzyme, spectroscopic colorimetric label, affinity tag, or nanoparticle.

5. The method of claim 1 in which the test compound is selected from a combinatorial library of solid support-attached test compounds comprising peptoids; random bio-oligomers; diversomers such as hydantoins, benzodiazepines and dipeptides;

vinylogous polypeptides; nonpeptidal peptidomimetics; oligocarbamates; peptidyl phosphonates; peptide nucleic acid libraries; antibody libraries; carbohydrate libraries; and small organic molecule libraries.

6. The method of claim 5 in which the small organic molecule libraries are libraries of benzodiazepines, isoprenoids, thiazolidinones, metathiazanones, pyrrolidines, morpholino compounds, or diazepindiones.

7. The method of claim 1 in which screening a library of solid support-attached test compounds comprises contacting the test compound with the target nucleic acid in the presence of an aqueous solution wherein the aqueous solution comprises a buffer and a combination of salts.

8. The method of claim 7 wherein the aqueous solution approximates or mimics physiologic conditions.

9. The method of claim 7 in which the aqueous solution optionally further comprises non-specific nucleic acids comprising DNA, yeast tRNA, salmon sperm DNA, homoribopolymers, and nonspecific RNAs.

10. The method of claim 7 in which the aqueous solution further comprises a buffer, a combination of salts, and optionally, a detergent or a surfactant.

11. The method of claim 10 in which the aqueous solution further comprises a combination of salts, from about 0 mM to about 100 mM KCl, from about 0 mM to about 1 M NaCl, and from about 0 mM to about 200 mM $MgCl_2$.

12. The method of claim 11 wherein the combination of salts is about 100 mM KCl, 500 mM NaCl, and 10 mM $MgCl_2$.

13. The method of claim 10 wherein the solution optionally comprises from about 0.01% to about 0.5% (w/v) of a detergent or a surfactant.

14. The method of claim 1 in which separating the detectably labeled target RNA:support-attached test compound complex formed in step (a) from uncomplexed target RNA and test compounds is by flow cytometry, affinity chromatography, manual batch mode separation, suspension of beads in electric fields, or microwave.

15. The method of claim 1 in which the library of solid support-attached test compounds are small organic molecule libraries.

16. The method of claim 15 in which the structure of the test compound is determined by mass spectroscopy, NMR, or vibration spectroscopy.

17. The method of claim 1 in which the library of solid support-attached test compounds are peptide or peptide-based libraries.

18. The method of claim 17 in which the structure of the test compound is determined by Edman degradation.